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The Newer Analgesic Drugs: Although morphine has been regarded for over a hundred years as the most effective and reliable compound for the relief of the more severe grades of pain, it has many undesirable properties. Morphine produces respiratory depression; it increases the activity and tone of the smooth muscle of the gastro-intestinal, biliary, and urinary tracts, causing constipation, spasm of the gall bladder and bile ducts, and urinary retention; it frequently causes nausea and vomiting; and it may induce itching of the skin. If morphine has to be administered over a long period of time, tolerance to the analgesic effect develops so that the dose must be increased from time to time to obtain adequate pain relief. Under such conditions of prolonged use, physical dependence on the drug develops. The euphoria induced by morphine, although likely a desirable action in that it may be necessary for pain relief, leads to overuse and addiction in persons with susceptible personalities.

Because of these undesirable actions, a constant search has been carried on for drugs which would be equal to morphine in analgesic action but which would have fewer side effects, and particularly for drugs which would have less addiction liability. Little progress was made until 1939 when Small, Eddy, Mosettig, and Himmelsbach issued a summary of their studies on methyldihydromorphinone, or metopon, a new member of the morphine series of drugs which appeared to possess some distinct advantages over morphine. Since 1939, two new potent analgesic drugs, which are not chemically related to morphine or to each other, have been discovered. These are meperidine, or demerol (ethyl 1-methyl-4-phenylpiperidine-4-carboxylate), and methadon, or amidone (6-dimethylamino-4-4-diphenyl-3-heptanone). The discovery of both these drugs must be credited to the German chemists and pharmacologists of the I. G. Farbenindustrie. It is because meperidine and metopon have much in common pharmacologically with each other and with morphine but lack resemblance structurally that great impetus has been given to the search for more effective analgesics.

Based upon the author's experience, when given in single doses, morphine and metopon are more effective than meperidine and methadon. However, if the drugs are used every from 4 to 6 hours, the order is radically altered. Methadon is a slowly acting, cummulative drug and, when repeatedly administered, exerts an effect on the reaction to pain equal to that produced by morphine and excels morphine in sedative and hypnotic effect. Methadon is, therefore, not a good drug for pre-anesthetic medication and is only fairly effective in situations requiring very rapid relief of pain, but it is a very good drug for the relief of chronic pain. Under conditions of repeated dosage, methadon is equal to morphine and metopon in inducing analgesia. Meperidine, though fairly effective, is not as reliable or as potent an analgesic as are the other three drugs.

In minimal analgesic doses, metopon is less likely to produce sedation and mental dullness than is morphine. Although respiratory depression is less marked

after the administration of metopon than after the administration of morphine, metopon, in conjunction with inhalation anesthetics, may produce serious respiratory depression and is, therefore, contraindicated as pre-anesthetic medication. Metopon is almost as effective in relieving pain when given by mouth as when administered hypodermically. Due to difficulties in manufacture, metopon is about 10 times as expensive as morphine, and the amount available for use may always be limited.

Meperidine is said to produce serious respiratory depression less often than does morphine. This statement seems to be based on clinical impressions or on counts of respiratory rate and not on actual measurements of respiratory minute volume. Nausea and vomiting are also claimed to occur less frequently than after morphine. If, however, one compares the figures published by Batterman on the incidence of nausea and vomiting after meperidine with those of Lee on the incidence of nausea and vomiting after morphine, it would appear that nausea and vomiting occur more often after meperidine than after morphine. Batterman gives the incidence of nausea after parenteral administration of meperidine to hospitalized patients as 8.4 percent and the incidence of vomiting as 3.8 percent; Lee found that the incidence of nausea after the subcutaneous administration of morphine was 3.5 percent and the incidence of vomiting was 2.3 percent. Despite these figures, it is common clinical experience that persons who cannot tolerate morphine because of nausea may tolerate meperidine. In man, meperidine relaxes spasm of the smooth muscle of the gastro-intestinal tract and the ureter. Although the role of the spasmolytic action of meperidine in relieving colicky pain has been over-emphasized, the drug at least does not increase spasm of smooth muscle as does morphine. Meperidine does not produce constipation. It is effective when administered by mouth, but is more expensive than morphine.

Methadon is very similar to morphine in all its pharmacologic actions. It depresses respiration as much as does morphine, causes nausea and vomiting just as frequently, and is constipating. It is quite irritating when injected subcutaneously, and, if injected repeatedly into the same sites, causes severe inflammation and induration of the skin. Nausea and vomiting occur so frequently after oral administration that the drug cannot be used by this route.

The danger of addiction is one of the most important matters which must be considered in evaluating the proper use of a new drug. Drug addiction can be defined as the abuse of a drug to such an extent that the individual has lost the power of self control with reference to use of drug, and to such an extent that the individual or society is harmed. Himmelsbach and Small have described addiction to the opiate drugs as consisting of three closely intertwined factors, namely, (1) tolerance, (2) physical dependence, and (3) habituation or psychic or emotional dependence. Tolerance may be defined as a diminishing effect on repetition of the same dose of a drug. Physical dependence refers to an altered

bodily state brought about by repeated administration of a drug which necessitates continued use of the drug to maintain physiological normality; it is manifest by the appearance of a characteristic illness when the drug is withheld. Habituation means psychic or emotional dependence on a drug - the substitution of the use of the drug for all other aims and objects in life. The extent to which these various factors are involved in addiction varies with the person and with the drug. Physical dependence has, in the past, been regarded as the most important quality of an addicting drug. Emotional dependence, however, is now believed to be the most important characteristic. It is the quality responsible for the initiation of addiction. A person becomes addicted, not because he needs the drug to prevent the appearance of a withdrawal illness, but because he enjoys the subjective sensations the drug produces. In assessing addiction liability the greatest weight should be given to the habituation liability of the drug in question.

Tolerance develops to many actions of metopon, methadon, and meperidine, including the sedative and emetic effects, and the pain threshold-elevating action. Partial tolerance to the respiratory and circulatory effects probably occurs. Tolerance to the clinical analgesic effects of all three drugs develops more slowly than does tolerance to the analgesic effect of morphine. The slow development of tolerance is the greatest advantage these drugs possess over morphine. Metopon has one further advantage: tolerance to the clinical analgesic effect of metopon is abolished by withdrawing the drug for only from 8 to 14 hours. This rapid loss of tolerance has not been shown to occur with any other analgesic drug.

Metopon, meperidine, and methadon all have physical dependence liability. When metopon or meperidine was substituted for morphine, signs of the abstinence syndrome were partially, but not completely, suppressed. Following withdrawal of metopon or meperidine after substitution for morphine, abstinence syndromes which were qualitatively similar to abstinence from morphine appeared very quickly. Symptoms of abstinence also developed following withdrawal of meperidine after administration of large doses to former morphine addicts for from 10 to 11 weeks, or after withdrawal of metopon after 21 days or more of administration to patients for the relief of chronic painful disease. Abstinence symptoms following withdrawal from both meperidine and metopon came on more rapidly, were less intense, and subsided more rapidly than did abstinence symptoms following withdrawal from morphine. Methadon completely relieved and suppressed signs of abstinence from morphine. Following withdrawal of methadon after substitution for morphine, or after administration to former morphine addicts for from 2 to 6 months, an abstinence syndrome developed which came on more slowly, was much less intense, and subsided more slowly than did the abstinence syndrome following withdrawal of morphine. The abstinence syndrome following withdrawal of methadon was milder than the abstinence syndrome following withdrawal of metopon or meperidine. Following withdrawal of methadon, very few of the autonomic signs so characteristic of the abstinence syndrome following withdrawal from morphine, metopon, or meperidine were observed.

Single minimal analgesic doses of methadon and metopon seldom produce significant euphoric reaction in either non-addicts or former morphine addicts. In the experience of the author and co-workers, despite the literature on the subject, single minimal analgesic doses of meperidine frequently cause mild euphoria. If, however, the drugs are administered in doses as large as one would expect addicts to use, both metopon and methadon produce grades of euphoria which equal, or exceed, those induced by morphine, and which are more intense than the euphoria after any dose of meperidine. The euphoria after large doses of metopon is maintained as long as euphoria following morphine, and the euphoria after large doses of methadon is sustained for from 36 to 48 hours. Euphoria after meperidine lasts only one or two hours. For this reason, meperidine is not as popular with experienced morphine addicts as are metopon and methadon. The behavior of men experimentally addicted to methadon was similar to that seen during morphine addiction. They ceased all productive activity, neglected their personal appearances, and spent a great deal of time in bed in a semi-somnolent state. Following withdrawal of methadon, the patients complained, begged for the drug, and would take additional doses months after all signs of physical dependence had disappeared. The behavior of patients addicted to meperidine is also similar to that of patients addicted to morphine.

The evidence forces the conclusion that all three drugs cause addiction. Any differences noted in the addiction liability of the new analgesic drugs from that of morphine are differences in degree, not kind. Tolerance has developed to actions of all three drugs. Physical dependence has been demonstrated after prolonged administration of all three drugs and, more important, all three drugs have been shown to possess considerable habituation liability.

Metopon and methadon have not been available for a sufficient length of time for nonexperimental addiction to them to occur. For some time a controversy was carried on concerning the addiction liability of meperidine. It was claimed that cases of addiction had not occurred in persons not formerly addicted to morphine (so-called "primary" addicts). This view is no longer tenable since a number of cases of primary addiction to meperidine have been reported in the literature. More than 20 persons primarily addicted to meperidine have been studied at the U. S. Public Health Service Hospital, Lexington, Ky. Their histories showed that their behavior was similar to the behavior of morphine addicts. They substituted the use of meperidine for all other aims and objects in life; they spent their savings for the drug, left their families for it, and lied, and stole to obtain it. In one respect, addiction to meperidine in these patients was more undesirable than addiction to morphine. The patients used such large doses that the serious toxic effects noted by Andrews - tremors, increased startle responses, and even epileptiform seizures - developed.

It is not to be expected that these new drugs will completely replace morphine. Due to its quick but long-lasting action, its reliability, its powerful sedative action,

and its relative cheapness, morphine is still the choice for most patients requiring relief of pain for periods of less than 14 days.

The use of metopon has been restricted by the National Research Council to persons with chronic painful diseases, and the drug is available for oral use only. This decision was taken because of the slow development of tolerance to metopon, the rapid loss of tolerance on short withdrawal, the low degree of sedation, its effectiveness by the oral route, and because of the limitation of the amount available due to difficulties in manufacturing.

Meperidine seems to have lost popularity because it is not as reliable or as long-lasting an analgesic as is morphine or methadon. Severe grades of pain are often not well controlled with meperidine. The drug, however, deserves a trial in cases of pain associated with spasm of smooth muscle. It is also indicated for persons who are nauseated by morphine. Because it is effective orally, and because tolerance develops slowly, it is quite useful in managing chronic diseases associated with mild grades of pain.

Methadon can be used in most situations in which morphine is indicated. Due to its slow cumulative action, it is probably not as desirable as morphine in situations demanding very quick relief of pain. The drug is useful in chronic diseases because tolerance develops slowly and physical dependence on the compound is quite mild. If a person with a chronic disease has received morphine for a long period of time, methadon is the only drug which can be satisfactorily substituted for the morphine because meperidine and metopon do not completely suppress signs of the abstinence syndrome following withdrawal from morphine. The fact that methadon cannot be used orally is a great disadvantage, which largely limits its use to patients under hospital supervision. Due to the low intensity of the abstinence syndrome following withdrawal of methadon after substitution for morphine in cases strongly addicted to morphine, methadon is the drug of choice for treatment of the morphine abstinence syndrome.

Meperidine, metopon, and methadon have been placed under the provisions of the Harrison Narcotic Act in order to minimize abuse of the drugs and to limit the spread of addiction to them. Physicians should keep the danger of addiction to these substances in mind and should exercise the same caution in prescribing them as is followed in prescribing morphine. The drugs should never be used when other drugs or other measures will suffice. The dosage should be held to the minimum compatible with adequate pain relief, and the interval between doses should be as great as possible. The drugs should be discontinued as soon as the need for pain relief has passed. They should never be used primarily for their sedative actions. In chronic cases, they should be administered orally whenever possible. Self medication with a hypodermic should be discouraged. The drugs should never be given intravenously because this method produces maximum euphoria and carries a great risk of addiction. The drugs should not be administered to persons with known psychopathic or psychoneurotic

personalities unless very definite indications for the use of a potent analgesic are present. The drugs should never be used for the relief of symptoms due to alcoholic excess because alcoholics are very prone to addiction. The drugs should never be used for the treatment of asthma because asthmatics are also very susceptible to addiction. It is significant that several of the patients with primary addiction to meperidine observed at Lexington, Ky., became addicted as a result of administration of meperidine for the relief of asthma. (Ann. Int. Med., Dec. '48 - H. Isbell)

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A Clinical and Experimental Study of Isuprel in Spontaneous and Induced Asthma: One of the synthetic analogues of epinephrine - 1-(3′, 4′-dihydroxyphenyl)-2-isopropylaminoethanol - has been studied under the name of "aleudrin" for a number of years in Europe. The experimental and clinical use of this drug in bronchial asthma and emphysema has been reviewed by Dautrebande, and a report has been published in this country by Charlier. The drug, administered as an aerosol, has been described as being especially effective in relieving attacks of bronchial asthma and significantly more active than epinephrine.

In this country Segal has reported excellent results in the treatment of bronchial asthma with the same preparation, but called "isuprel," and Siegmund et al. found this drug to be the most active of a number of structurally related compounds in a study in guinea pigs using histamine and horse serum.

The authors have had occasion to observe the efficacy of isuprel in asthmatic patients in the outpatient clinic, among private patients on the hospital wards, and, also, in association with experimental studies involving the induction of asthma-like attacks with histamine, acetyl-beta-methyl choline (methacholine), and certain allergenic extracts.

Isuprel was made available as a solution for administration by aerosol in a concentration of 1 and 0.5 percent, in a concentration of 0.02 and 0.01 percent for injection, and in tablets containing 10 mg. for sublingual administration. The effectiveness of these preparations in relieving the signs and symptoms in asthmatic subjects was studied.

Asthmatic subjects using this agent were observed for relief of asthma on the hospital wards or at home. The effectiveness of treatment was judged chiefly by statements made by the patients and to a lesser extent by changes in physical signs. The use of other preparations was not specifically discouraged, and there were frequent cases in which the efficacy of isuprel could be compared with that of other agents with which the patient was familiar.

Subjects with asthma were observed in the laboratory during spontaneous attacks, and changes in vital capacity and physical signs, as well as the degree of subjective relief, were observed after the administration of isuprel.

Similar observations were made in asthma-like attacks induced by exposure to aerosolized allergenic extracts, histamine and methacholine and by injections of histamine and methacholine according to technics that have been described elsewhere.

The vaponephrin nebulizer or the No. 40 DeVilbiss nebulizer was used with a hand bulb by patients treating their asthmatic attacks outside the hospital, and these nebulizers supplied with pressure from an oxygen tank with the flow meter adjusted to read from 6 to 8 liters per minute were also used on the ward and in the laboratory. Although the No. 40 DeVilbiss nebulizer may be somewhat less efficient than the vaponephrin nebulizer, the authors observed no difference between the two types in these studies.

During administration of the various aerosols used in this study, patients were instructed to exhale forcibly, then to make a maximum inhalation and finally to hold their breath for a few seconds before exhaling. Vital capacity measurements were made in the usual manner, and tracings of the expiratory curves were made on a moving drum. Care was taken to ensure maximum effort on the part of the patient. Maximum ventilatory volume was determined by the method of Hermannsen, which has been discussed in detail by Cournand, Richards, and Darling. A 9-liter Benedict-Roth type of metabolism apparatus was used, equipped with special low-resistance valves and with the container for soda lime removed. Computation of results was simplified by the addition to the machine of a recording ventilometer that measured inspiratory volume only. A maximum ventilatory effort was made for fifteen seconds with the patient choosing his own rate and depth of respirations. Normal values for this method are approximately 150 liters per minute for male and 100 liters per minute for female subjects.

Thirty asthmatic patients were supplied with isuprel in a concentration of 0.5 percent to be administered with a hand nebulizer at home. Ten of the 30 patients using the drug at home obtained excellent relief, 14 obtained good relief, 3 obtained fair relief, and 3 obtained practically no relief.

Ten of these 14 patients classified as having received good relief with isuprel stated that this was true only when the attacks of asthma were not severe. While under observation and using isuprel at home, 7 of these patients developed severe asthma and required hospitalization. In this group 3 other patients, although they were not hospitalized, developed severe asthma with no benefit from isuprel and had to be treated by other measures. It could not be determined why these changes occurred, but the severity of the asthma may have been the determining factor.

In addition to the 7 patients who had been using isuprel at home before hospitalization, there were 5 patients with severe asthma who received isuprel for the first time in the hospital. Of these 12 patients, 10 required, in addition to isuprel, intravenous injections of aminophylline, repeated doses of sedatives including demerol, infusions of glucose and saline solution, epinephrine and in some of these 10 patients, oxygen with or without helium was also used.

The patients were not encouraged to continue using isuprel when repeated administration gave only very brief and incomplete relief. The authors are aware that much more intensive and prolonged administration of isuprel aerosol has been reported to be successful under these circumstances. When continued administration failed to produce subjective or objective improvement in these patients, the authors abandoned this method of treatment and relied upon the procedures mentioned above. Patients in whom isuprel aerosol had become ineffective in relieving the more severe attacks of asthma frequently found that relief with isuprel was obtained from milder attacks occurring subsequently.

Two patients with severe asthma died unexpectedly. The cause of death appeared to be asthma. The authors were unable to determine what part, if any, isuprel played in these cases.

Observations were made in 23 subjects with spontaneous asthma. The vital capacity of each subject was determined, and any change after inhalations of isuprel was observed. An increase in vital capacity occurred in every case, and this was usually associated with subjective sensations of relief. As a rule the physical signs of asthma decreased, but in one case they increased in spite of a rise in vital capacity and a reduction in the subjective sensation of asthma. In most cases in which small increases occurred, the vital capacity was close to the maximum vital capacity for the patient, as judged by values obtained at periods when no asthma was present.

In a few cases there was opportunity to compare the efficacy of isuprel administered by inhalation with that of epinephrine by inhalation (1:100 solution) and injected subcutaneously (1:1000 solution) and aminophylline given intravenously. It was recognized that patients may overestimate the efficacy of a new preparation when it is first used and that some of the stated results is perhaps best regarded with this tendency in mind.

One subject received five inhalations of epinephrine 1:100 with an increase in vital capacity from 2150 to 2700 c.c. A second series of 5 inhalations caused a further rise of only 50 c.c. The subcutaneous administration of 0.3 c.c. of epinephrine (1:1000 solution) caused no further increase in vital capacity in a period of ten minutes. Five inhalations of isuprel (one percent) then caused an increase to 3050, and a second series of 5 inhalations caused a further increase to 3700 c.c.

In another patient receiving isuprel for the first time, inhalations of the drug (one percent) were given repeatedly over a period of thirty minutes. Marked relief of asthmatic symptoms occurred - the best in many weeks. On the following day the inhalations were repeated, but epinephrine (1:100 solution) was substituted for the isuprel without the patient's knowledge. Little relief occurred, and the patient was greatly disappointed. On the third day isuprel was given again with excellent relief. No vital capacity studies were made in this patient.

Although most patients who used both epinephrine and isuprel as aerosols stated that the latter was consistently superior, 4 patients stated that epinephrine was as good as isuprel or better, after having had considerable experience with both. The epinephrine preparation used in some cases was a proprietary product containing the drug in a concentration of 2 percent.

On numerous occasions patients who were admitted to the hospital for treatment of asthma received both isuprel by inhalation and aminophylline intravenously in doses of 0.25 or 0.48 Gm. Although no studies of vital capacity were made, the very definite impression was obtained that aminophylline injected intravenously was superior to isuprel for the treatment of severe asthma. Subjective relief was not only greater but also more prolonged. Experience with aminophylline given by other routes has been limited and is difficult to evaluate.

Observations were made in 9 asthmatic subjects in whom asthma-like attacks were induced by exposure to various aerosolized allergenic extracts by inhalation. The administration of isuprel caused a rapid return of the vital capacity readings toward normal. In some cases pyribenzamine or atropine had been given with a view to possible protection of the patient from the expected decrease in vital capacity or in an attempt to restore the vital capacity after this had been reduced by exposure to an aerosolized pollen extract. Isuprel was effective in every case but one, whereas intravenously administered atropine was without influence or had a very slight effect and intravenously administered pyribenzamine rarely influenced the vital capacity under the circumstances of the tests. Interpretation of results obtained with tests of this kind is complicated by the tendency of the vital capacity to return toward normal without any treatment. However, inspection of the records obtained in these experiments afforded convincing evidence that inhalation of isuprel was chiefly responsible for the observed rapid increases in vital capacity.

Experiments were carried out in which the effect of isuprel administered parenterally on two occasions and by aerosol on another occasion was observed for evidence of any resulting change in the subjects' susceptibility to injected histamine or methacholine as determined by changes in vital capacity.

These studies, though few in number, indicate that isuprel furnishes potent protection against the reduction in vital capacity and asthma-like attacks induced by the parenteral administration of histamine and methacholine. The authors' experience with the intramuscular use of isuprel is limited, but the short-lived protection afforded against histamine and methacholine together, with the degree of side reactions produced by the drug as compared with intramuscular injections of epinephrine, discouraged them from further studies.

The authors' experience with the sublingual use of isuprel is limited to observations in 13 patients receiving the drug by this route for relief of symptoms at home and in 2 subjects studied in the laboratory.

Patients receiving tablets of isuprel sublingually at home were instructed to take one tablet containing 10 mg. at thirty minute intervals until relief had occurred or until four tablets had been taken in any one day. Of these 13 patients, 3 who were suffering from mild asthma stated that they had obtained excellent relief after taking one or two tablets. Five patients had asthma of moderate severity, and of these, 2 stated that the drug was without effect, and the remaining 3 obtained relief of very short duration even with doses as large as 50 mg. in two hours. The 5 remaining patients who had severe asthma denied benefit with similar doses.

Two patients with spontaneous asthma were studied in the laboratory. These two experiments suggest that isuprel was not very effective when administered by the sublingual route, except perhaps with large doses. No side reactions were experienced with doses of 50 and 70 mg. respectively despite the fact that palpitation and tachycardia were noted after intramuscular doses of the drug as low as 0.1 mg. The authors recognize the possibility that the physical characteristics of the sublingual tablets and the success patients may have in preventing themselves from swallowing while holding the tablet under the tongue are important factors in the results obtained in studies of this kind.

Only 2 patients in this series of 30 asthmatic subjects experienced symptoms that might reasonably be attributed to inhalation of isuprel. In each case, nervousness, tachycardia, and palpitation, lasting only a few minutes, were experienced. In one case this followed 15 inhalations of isuprel (1:100 solution), and in the other, these symptoms followed repeated groups of from 5 to 10 inhalations of isuprel (1:200 solution) at short intervals. Both patients used isuprel on other occasions without difficulty.

In the administration sublingually, no side reactions other than a bitter taste were observed in the 15 patients receiving tablets containing 10 mg. of isuprel in amounts up to 70 mg. within a period of an hour or more. A normal subject receiving one 10 mg. tablet sublingually experienced flushing and headache with slight malaise lasting about an hour.

In 5 cases in which isuprel was given subcutaneously or intramuscularly, side reactions were observed. These were tachycardia, palpitation, and nervousness in all cases, a fall in blood pressure in one case and pallor, nausea and a rise in blood pressure in another. These reactions were not associated with any change in the lung that could not have been readily obtained with isuprel administered by aerosol or with other agents causing fewer or no side effects.

It is considered that isuprel given as an aerosol was very effective in relieving mild or moderately severe asthma and appears to be the most effective agent available for self-medication. (New England J. Med., 13 Jan. '49 - F. C. Lowell et al.)

A Drug Sensitizing the Organism to Ethyl Alcohol: Experiments with tetraethylthiuramdisulfide [bis(diethylthiocarbanyldisulfide)] in the biological laboratories of Medicinalco, Copenhagen showed that people who had ingested from 0.5 to 1.5 Gm. of this substance (an otherwise inert dose) developed characteristic symptoms when they subsequently drank even small amounts of alcohol. These symptoms include a feeling of heat in the face, followed by an intense flushing, located principally in the face but spreading in some cases to the neck and upper part of the chest and arms or even to the abdomen. A constant effect is dilatation of the scleral vessels, making the person look "bull-eyed." These are followed a little later by palpitations, and sometimes slight dyspnea. After larger doses of alcohol, nausea and vomiting often develop. If nausea is intense, blushing gives way to pallor. These symptoms, which are usually accompanied by headache, are very unpleasant. They disappear, however, within a few hours, generally leaving the person rather sleepy. After the alcohol has been oxidized, the person feels completely well again, and all complaints are usually relieved by a short nap.

Similar symptoms follow the intake of alcohol combined with some other drugs, the best known of which is cyanamide. Ingestion of the fungus Coprinus atramentarius in combination with alcohol gives rise to similar symptoms.

Tetraethylthiuramdisulfide (trade name, "antabuse") is relatively nontoxic. The lethal dose in animals is reported to be 3 Gm. per kg. of body weight. In experiments in the authors' laboratory, daily doses of 10 mg. were given to rats, and 60 mg. to rabbits, for more than three months without any notable effect on the blood picture or otherwise. In clinical trials single doses of up to 6 Gm. and daily doses of from 0.25 to 0.60 Gm. for several months were given without producing any subjective or objective symptoms apart from those following the ingestion of alcohol.

Normal people usually show no effect or only slight symptoms after taking from 10 to 20 Gm. of alcohol (from 30 to 60 ml. of gin), but, if a person has taken from 1.0 to 1.5 Gm. of antabuse the previous day, symptoms develop involving mainly the circulatory and respiratory systems. Circulatory effects are the facial vasodilatation already described, pulse rate raised to from 120 to 140 per minute, and a slightly increased cardiac output. No significant change in blood pressure has been observed, except for a slight fall in a few instances. Respiratory effects include an increase in the dead space, increased pulmonary ventilation, and a corresponding reduction in alveolar carbon dioxide.

The effects start from 7 to 12 minutes after the ingestion of alcohol and are maximal after about 30 minutes. Flushing is the most sensitive symptom and is generally seen with a blood-alcohol level of about from 15 to 20 mg. per 100 ml. The increase in ventilation and pulse rate is first noted when the blood-alcohol level reaches at least from 25 to 40 mg. per 100 ml.

In experiments on animals, Larsen noted no definite effect on blood pressure, but pulmonary ventilation increased from 20 to 35 percent after the administration of alcohol to animals previously treated with antabuse, whereas no change was seen in untreated animals given the same dose of alcohol.

The characteristic effect of alcohol does not appear unless the antabuse is taken at least three hours earlier; in some clinical trials this latent period was as long as forty-eight hours.

The absorption of antabuse from the gastro-intestinal tract is not complete. In human beings, about 20 percent of a given dose is excreted in the feces during the following two or three days, and the same tendency is seen in rabbits and dogs. The elimination of antabuse is very slow in man. No antabuse is excreted unaltered in the urine, and after the intake of from 1.5 to 2.0 Gm. by mouth no increase in the S/N ratio was detected in the urine during the next eight days.

Owing to the slow elimination the effect of a single dose lasts rather a long time. If the increase in skin temperature after the intake of 40 ml. of gin is taken as an indicator, the action of 0.5 Gm. of antabuse lasts three or four days, 1.0 Gm. five or six days, and 1.5 Gm. seven or eight days.

No experiments have yet been done to find out if the protracted action is due to slow absorption from the intestinal tract or to fixation in the tissues after absorption. The latter alternative is the more probable.

Concerning the mode of action, the symptoms can be fully explained by an increased formation of acetaldehyde after the taking of alcohol by people previously treated with antabuse. Small amounts of acetaldehyde are found in the blood even in normal people after taking alcohol. In people who have taken antabuse, the blood acetaldehyde level rises to about from 2 to 5 times that in normal people who have taken the same dose of alcohol. Further, up to nine times as much acetaldehyde can be isolated and identified as 2, 4-dinitrophenylhydrazone from the expired air of antabuse-treated people as in normal people given the same amount of alcohol under the same conditions.

Handovsky has shown that acetaldehyde increases the ventilation and heart rate, but it is not known at what blood acetaldehyde levels these effects appear; nor do the few published reports on the pharmacology of acetaldehyde describe its effect on the peripheral vessels in man. By means of continued intravenous infusion of acetaldehyde, Asmussen et al. have shown that at blood-acetaldehyde levels corresponding to those found in antabuse-treated people after taking alcohol, the same qualitative and quantitative effects are elicited, namely, flushing of the face and upper part of the chest, increased ventilation, reduced alveolar

carbon dioxide, raised pulse rate, and an increased dead space. Even in rabbits Larsen observed increased ventilation at blood-acetaldehyde levels corresponding to those found in antabuse-treated animals given alcohol. Acetaldehyde accumulates very rapidly after the intake of alcohol in antabuse-prepared animals; within 3 minutes after the intravenous administration of alcohol to antabuse-treated rabbits a considerable increase in blood acetaldehyde was noted.

It is difficult to explain why antabuse causes acetaldehyde to be formed in higher concentrations than normal after the ingestion of alcohol. The elimination rate of alcohol as measured by blood alcohol levels was the same in normal people and in people treated with antabuse. In rabbits also no difference between the two groups was observed. The authors' experiments show that acetaldehyde is eliminated at the same very rapid rate regardless of whether the animals have been treated with antabuse or not. This observation accords well with the fact that the blood acetaldehyde level is not raised in antabuse-treated animals before the administration of alcohol.

It must then be supposed that only part of the alcohol consumed passes, during oxidation, through the intermediate stage of acetaldehyde. In vitro experiments made by Lutwak-Mann support this suggestion. Perhaps after treatment with antabuse, the normal elimination of alcohol is partly or completely blocked, and under the influence of the alcohol dehydrogenase a higher portion of alcohol than normal is oxidized to acetaldehyde. Another possible explanation is that the alcohol hydrogenase is highly activated by antabuse, but further experiments are needed to solve this problem.(Lancet, 25 Dec. '48 - J. Hald and E. Jacobsen)

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Treatment of Alcoholism with a Sensitizing Drug: Hitherto, treatments for chronic alcoholism have given poor or transient results. Psychological treatment has been the most successful, and except for the use of apomorphine in the aversion treatment, no drug has proved at all effective. However, the discovery by Hald and Jacobsen (see foregoing article) that the intake of tetraethylthiuramdisulfide (antabuse) sensitizes the organism to even moderate doses of alcohol, makes it possible to develop a medical treatment for alcoholism. The author's studies on the effects of antabuse in alcoholics had run for about six months at the time of preparing this report, and, though this is far too short a time for a full assessment, the results in 74 out of 83 alcoholics seen since December, 1947 seemed promising enough to be worth publishing.

So far no harmful systemic effects on liver, heart, kidney, or blood-forming organs have been observed; nor have any untoward side effects been noted which could be attributed to antabuse.

After careful physical examination and study of the medical, psychiatric, and social background, the patient is given from 1.0 to 1.5 Gm. of antabuse and

is told to continue with 0.5 Gm. daily. He is told that he will become ill if he drinks alcohol, and is asked to return for a second interview two or three days later. The patient takes two or three drinks either the night before or immediately before the second interview to show the effect of the treatment. Sometimes the patient will already have taken the alcohol before this time, often in larger amounts than recommended and with a violent reaction, which is beneficial from a therapeutic point of view. A few patients, mostly heavy drinkers, can take considerable amounts of alcohol before the effect appears. In such cases, the medication is continued and the patient is tested in the same way at intervals of from four to six days. The tolerance for alcohol is, however, gradually reduced.

Thus, for example, after taking antabuse 1.5 Gm. the previous day and 0.5 Gm. the same morning, a heavy drinker took nine drinks (under control) during an hour. He blushed and had a raised pulse rate but nevertheless wanted to continue drinking. Five days later he was tested again and took 26 drinks before he had an explosive and copious vomiting. After the second test he was discharged from the hospital but continued the treatment. A few days later, after only two drinks, he had to break away from a lunch with his fiancee in a restaurant and take a taxi home. A few days later he became ill even after a single drink.

Such patients are exceptions; most feel so uneasy after four or five drinks taken in one or two hours that they never want to repeat the experience.

When the characteristic effect is observed, the patient is told to continue the treatment and is seen at least once a week at first and at longer intervals later on. It is very important for the patients to keep in contact with the doctor, or for their relatives to report to him, so that the effect of treatment can be controlled. In milder cases the patient sees the doctor in his consulting room, but sometimes it is necessary for the doctor to visit the patient's home.

The 83 patients reported upon here sought treatment more or less voluntarily. They are divided into four groups:

Group A. The 32 patients in this group benefited sufficiently from the treatment to continue on a token dose (often only 0.0625 Gm. a day) after a few weeks' observation period. Later their treatment was controlled by telephone. These patients can increase their dose when they know they will be tempted to drink.

Group B. The 29 patients in this group see the doctor in his consulting room at regular intervals and are encouraged to continue the treatment. Their blood and urine are examindd, and further dosage is fixed to meet each patient's requirements. The dosage in this group must be sufficient to prevent the patient from taking more than one or two drinks at a time.

Group C. The 13 patients in this group are more psychoneurotic than those in groups A and B and are therefore more difficult to follow. Their desire to be treated is not always genuine, and it often requires an effort on the part of the doctor and the patients' relatives to make them continue the treatment. The general impression is that even these difficult subjects have been helped to some degree, but a very long observation time is necessary before definite conclusions can be drawn. No doubt the treatment would be still more effective if legal measures could be taken, but, for the present, this is impossible in Denmark, in contrast to Sweden and Norway.

Group D. In 9 cases the treatment has failed. Most of these patients have serious psychic defects. All of them have shown the characteristic symptoms after intake of antabuse and alcohol, but they have lacked interest in the treatment and have refused to continue it.

The follow-up is still too short to ascertain how long the results will last, or if any undesirable side-effects will follow the protracted use of antabuse. For this reason caution is advised in treating patients with organic diseases. So far, however, the treatment is promising, especially for the habitual drinker.

The treatment with antabuse must often be only part of a general treatment. In severe cases psychological analysis and psychotherapy are important, as always, in the treatment of alcoholism. (Lancet, 25 Dec. '48 - O. Martensen-Larsen)

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Convulsions During Anesthesia: Convulsions which develop during an operation are frequently the first sign of a serious, and occasionally fatal, complication. The problem of convulsions during anesthesia has been primarily the concern of the anesthetists. It has become increasingly evident, however, that, in cases in which convulsions occur, many factors in the care of the patient prior to operation, during operation, and following operation are the responsibility of the surgeon.

In 1937, Lundy reviewed 144 cases from the literature. He listed a large number of causative factors. His study revealed a mortality rate of 18.9 percent.

Convulsions occurring during administration of nitrous oxide, followed by postoperative encephalopathy and death, are generally accepted as due to anoxemia and cerebral anoxia. However, anoxia in all probability is a major factor in convulsions during other forms of inhalation anesthesia.

In addition to the occurrence of convulsions, there are other less frequent complications and sequelae of inhalation anesthesia, namely, (1) sudden death under anesthesia, (2) delayed death, usually following a period of coma and

repeated seizures, and (3) survival with permanent or transitory neurologic manifestations. Although instances of the latter type, namely, survival with permanent neurological damage are not common, more have occurred than are reported in the literature.

A case of permanent cerebral cortical damage and generalized spastic paralysis following cyclopropane anesthesia for appendectomy has come to the authors' attention and prompted this report. A study of the literature reveals no similar sequelae of this particular anesthetic agent. Taylor's report of 33,777 cases of the administration of cyclopropane with convulsive movements in 39, or 0.1 percent, indicates the safety of this agent when employed by an anesthetist well trained in its use.

In an analysis of the causative factors of the convulsions in the patient reported upon by the authors, it is noted that the patient was a female child with extreme dehydration and toxicity due to appendicitis with perforation. There was a history of persistent vomiting of 48 hours' duration. On the day of operation, the temperature of the atmosphere was 100° F., and the barometric pressure, 29.261 inches. A possible source of further faulty oxygenation in the patient's tissues is found in the use of an adult-type mask and tubing; therefore, a "dead space" was created in the closed system used with cyclopropane.

Prevention of the complications of anoxia during inhalation anesthesia consists of careful evaluation of the pulmonary, cardiovascular and renal systems of each patient prior to operation. Dehydration and acid-base imbalance should be corrected preoperatively by the proper parenterally administered fluids. Over-heating of the patient in the operating room is to be avoided. Anemic patients should be given transfusions to achieve normal red cell and hemoglobin values. Preoperative medication should be individualized to prevent oversedation or undue excitement. The proper administration of the anesthetic agent is of primary importance. Prolonged operative procedures and undue trauma in the poor-risk patient should be avoided.

With the occurrence of convulsions, it is necessary that one act quickly to correct the anoxia. The operation should be terminated promptly. The anesthetic should be discontinued. Oxygen should be administered with the assurance that an adequate airway is open. Soluble barbiturates should be given to control the convulsions. Fluid and electrolyte balance must be maintained and compensation made for the blood loss. Hyperthermia may be allayed by sponging with water or alcohol or by fanning. When the convulsions are brought under control, the patient must be observed for signs of recurrence, oxygen therapy continued, the temperature kept below 102° F., and the electrolytes kept in balance by parenterally administered fluids.

In the discussion, Dr. John M. Waugh, Rochester, Minn., stated that Doctor Lundy had seen the report and considered that the case was a typical one of

convulsions under general anesthesia. Doctor Waugh credited the authors for, first, emphasizing the condition under which the distressing complication is likely to arise and, second, pointing out that the condition is amenable to treatment when it is instituted early. He stated, however, that unfortunately, it will occasionally occur, as Doctor Lundy has pointed out, during anesthesia without any cause whatsoever in a patient in excellent condition. About five years ago, Doctor Waugh had 2 patients the same morning in the same operating room with the same team. Both had convulsions under general anesthesia, which were recognized and treated, and the patients suffered no untoward results. In both instances the operation was of considerable magnitude, and at a point where it would have been impossible to terminate the procedure. Doctor Waugh stated that Doctor Lundy and Doctor Mousel pointed out in Anesthesiology in 1945 that they had been able to isolate from the nasopharynx in patients suffering convulsions in anesthesia a streptococcal organism which when inoculated in experimental animals produced spasms which were much severer under nitrous oxide and oxygen-ether anesthesia. Only further experimentation will prove whether this is significant. He said that Lundy has observed that 3 c.c. of 2.5 percent "sodium pentothal" (sodium 5-ethyl-5-1-(1-methylbutyl) thiobarbiturate) given intravenously is sufficient to control the convulsions. Doctor Waugh believes that it is important for all to point out to residents and interns in various hospitals the fact that these convulsions do occur, even now with proper preoperative preparation, and it is extremely important to have sodium pentothal available for immediate administration. (Arch. Surg., Sept. '48 - E. L. Strohl and F. E. Sarver)

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The Millikin Oximeter in the Recognition and Treatment of Anoxemia: The Millikan oximeter affords a simple and accurate means for determining the changes in arterial oxygen saturation, at the bedside, without the discomfort of arterial puncture, or the difficulties of conventional gas analysis. The authors have used it on the medical wards of the Hospital of the University of Pennsylvania to assess the need for oxygen therapy in the individual patient, and to determine the method of oxygen administration best suited to his needs.

The oximeter consists essentially of a small ear unit and a galvanometer. The ear piece contains an electric bulb, light filters, and a photo-electric cell. It fits over the pinna of the ear with the bulb in front, the filters and cell behind. The heat generated by the bulb dilates the arterioles of the ear and increases the blood flow sufficiently to make the ear blood equal, in oxygen content, to arterial blood. The light generated by the bulb penetrates the ear and strikes the photo-electric cell. The filters and cell have such characteristics that variations in the amount of oxyhemoglobin within the blood vessels of the ear are recorded continuously on the galvanometer. Present models of the instrument cover only half the potential range of saturation; hence the galvanometer is graduated from 50 to 100 percent. There is a time lag of 5 seconds in the

galvanometer. With these limitations, Millikan has shown by comparison with hundreds of simultaneous arterial punctures, that the instrument is accurate within from 3 to 7 percent.

Although percentage changes in oxygenation can be read directly from the instrument, absolute values can only be obtained by one of two procedures: (a) while a normal subject is breathing 100 percent oxygen, the galvanometer is adjusted to a reading of 100 percent; subsequent changes in the same subject during the same experiment will be shown in absolute figures; (b) with an abnormal subject whose capacity to oxygenate his blood completely in an atmosphere of pure oxygen is questionable, the galvanometer must be set at some arbitrary figure and simultaneously one arterial blood sample for gas analysis must be taken; the mathematical difference between the arbitrary setting and the actual saturation at that moment can then be used as a constant factor for correcting subsequent readings during the same run.

Changes in arterial oxygen saturation were measured by means of the Millikan oximeter in 10 normal subjects and 36 patients with cardiac and, or, pulmonary disease (a) breathing room air, and (b) breathing from 90 to 97 percent oxygen. The normal oximeter response which was observed as a result of the subject changing from room air to from 90 to 97 percent oxygen was 5 percent or less. Patients suffering with a combination of both pulmonary and cardiac disease showed the most marked oximeter response to oxygen therapy. Those with extensive pulmonary disease, or pulmonary edema secondary to cardiac failure, showed moderate response. Patients with acute cardiac infarction showed relatively small responses, although the majority (75 percent) were above the normal range.

The figures show that, whereas in general the largest oximeter responses were obtained with the highest concentrations of inspired oxygen, certain patients showed very striking responses to lower concentrations.

Thus in selected cases, the relatively low inspired oxygen concentrations such as are obtainable in an oxygen tent or by nasal catheter, appear to be therapeutically effective. However, the selection of such cases on clinical grounds alone does not seem possible.

If it had not been for the oximeter, the patient described in case report 36 might not be alive today. This 44-year-old man with advanced pulmonary fibrosis had been admitted to the medical wards 4 times between March 1946 and January 1947 for congestive heart failure. In February, 1947, he was readmitted very ill with anasarca, orthopnea and cyanosis. He was tested with the oximeter and a remarkable response (45 percent) was obtained with from 90 to 97 percent oxygen administered by B. L. B. mask. This was checked by means of chemical determinations of arterial oxygen saturation, and found to be accurate. Then by means of the oximeter it was determined that as little as 33 percent oxygen in

the inspired air would maintain a from 30 to 35 percent rise in the oximeter reading. Consequently, he was placed on continuous oxygen by nasal catheter at 6 liters per minute, digitalization was maintained, diuretics discontinued, and his fluid intake was not restricted. A marked clinical improvement occurred. At the end of 3 weeks he was discharged, free of edema, and with no dyspnea while walking slowly. During the eleven months since then, he has led a more or less ambulatory life at home, remaining free of congestive heart failure by using nasal oxygen throughout the night, and stopping it during the day. Digitalis has been continued. Thus, the oximeter led to the discovery that a marked rise of arterial oxygen saturation could be obtained in this patient by the relatively low inspired oxygen concentrations obtained by nasal catheter; this resulted in the institution of a practical and effective method of treatment.

One rather unusual reaction to oxygen therapy was encountered. A 58-year-old male with emphysema and chronic bronchitis was admitted to the hospital acutely ill with extreme cyanosis; temperature 100.2°, dyspnea and orthopnea. Roentgenograms of his chest revealed an extensive bilateral bronchopneumonia in addition to the pre-existing pulmonary disease. He was conscious, but slightly disoriented on admission. Oxygen therapy was started coincidently with the oximeter run. After 5 minutes of breathing from 90 to 97 percent oxygen, the patient became deeply comatose. His blood pressure rose to 180/100 from a preoxygen level of 130/70. He showed a 30 percent oximeter rise. When oxygen was stopped, he regained consciousness and his blood pressure fell to its admission level. This series of events could be repeated at will. With nasal oxygen at 7 liters a minute, his oxygen saturation rose approximately 20 percent, and he did not become comatose. Consequently, it was decided to use nasal oxygen for treatment instead of a B. L. B. mask. With massive antibiotic therapy and nasal oxygen, he made a rapid recovery. After resolution of his bronchopneumonia, as judged by both x-ray and clinical signs, a final oximeter run revealed a response of 12-1/2 percent. He was still slightly cyanotic, as he had been on examination one year previously. Such unusual reactions to oxygen therapy have been described in individuals with chronic anoxemia. These patients are thought to develop a tolerance to oxygen lack by means of changes in the cellular metabolism of their cerebral tissues. Thereafter a sudden increase in arterial oxygen tension may give rise to such symptoms of central nervous system disturbance as somnolence, semi-coma or coma which may last for several days.

There are certain clinical factors (type of disease, presence of pulmonary congestion, cyanosis) which are of some help in predicting and in evaluating the results of oxygen therapy. However, in many instances the results of oxygen inhalation cannot be predicted, nor can they, as a rule, be accurately evaluated by ordinary clinical methods. The oximeter permits the evaluation of results; it has not helped much toward making it possible to predict the results.

An oximeter response which is significantly greater than the normal may be accepted as evidence that anoxemia is present and signifies that therapeutic benefit may be expected from oxygen therapy, roughly commensurate with the degree of the response. However, the converse is not true - a normal oximeter response does not rule out the presence of anoxemia. For instance, a lesion, in which blood enters the left side of the heart without first coming into contact with aerated lung, will produce anoxemia, which will not show a striking response to the inhalation of oxygen. The authors have observed this failure to respond in a very cyanotic child with the tetralogy of Fallot. Arterial puncture revealed an arterial oxygen saturation of 53 percent while breathing room air. Oxygen inhalation of 5 minutes' duration gave a rise of only 5 percent in the oximeter reading. Another subject with an undiagnosed type of congenital heart disease showed only a 6 percent response to oxygen therapy despite deep cyanosis.

Stagnant anoxemia due to slow circulation, in which blood leaves the heart with a normal oxygen saturation, but passes slowly through the capillary bed and returns to the heart with a very low saturation, theoretically would not show a marked response to oxygen inhalation. This might explain why the responses seen in acute cardiac infarction were relatively small.

It is not believed that a small or normal oximeter response necessarily signifies that oxygen therapy is useless if other indications for it exist. In such critical situations as severe myocardial infarction, even a slight increase in the oxygen available to the damaged tissues may be beneficial. When such a patient is given a high concentration of oxygen to breathe, a certain quantity of oxygen is dissolved physically in the plasma in addition to the measurable increase in oxyhemoglobin. The sum represents a substantial increase in the oxygen available for utilization. However, a patient with a small oximeter response is probably less likely to derive benefit from oxygen therapy than a patient with a great response.

The value of oxygen therapy to prevent anoxemia in anesthesia, postoperatively and in elderly individuals with pulmonary disease, is well established. In such cases the oximeter may be of value in detecting small degrees of anoxemia, although ideally oxygen therapy should be instituted prior to the development of anoxemia.

The oximeter may be used in negroes, but preliminary tests suggest that the magnitude of the change in the oximeter reading is less than the actual change in arterial saturation.

The oximeter enables the physician at the bedside to determine the effectiveness of oxygen therapy more accurately than by clinical evaluation, and in certain instances permits him to recognize the presence of anoxemia which might otherwise have been overlooked. (Am. J. M. Sc., Dec. '48 - L. Godfrey et al.)

Effects of Electrolyte Imbalance on the Adrenal Gland: When the adrenal cortex atrophies or is removed, the sodium content of the body decreases and the potassium content increases.

Many studies have been made on the amounts of sodium and potassium required by the normal body. In these studies the histologic aspects of the adrenal gland have been neglected; however, there are a few recorded observations.

It has been noted that changes occur in the adrenal gland after administration of a diet deficient in sodium or in potassium; this is not surprising since the adrenal gland is known to have a profound influence on the metabolism of these substances. Kornberg and Endicott, using a potassium-deficient diet, found that the adrenal gland showed "hydropic" changes. Schrader, Prickett and Salmon, also using a potassium-deficient diet, found marked congestion of the adrenal glands. They also noted that the cortical cells stained poorly and appeared rarefied and edematous. Orent-Keils, Robinson and McCollum, using a sodium-deficient diet, reported: "The adrenals were orange in color and contrasted with the pale pink of the controls; they were smaller in every case.... The change in color of the adrenals is especially noteworthy." There have been no further observations or explanations.

In view of the close chemical relation of the cholesterols of the adrenal gland and the hormones elaborated by the gland, it is assumed that the hormones are formed from the cholesterols. Levine, Darrow and Sarason, Dalton and coworkers and others have shown that in anoxia there is marked depletion of the cholesterols, especially in the inner zones of the gland. This is true with many kinds of physiologic stress. Concurrently with this, Hoagland observed an increase in the urinary output of 17-ketosteroids; he considered the adrenal gland as the major source of these compounds. From this one would expect to find depletion of cholesterols in the area of the gland which was suddenly called on to produce a hormone. This is the case in the experiments reported here.

It has been demonstrated by Smith, Crooke and Gilmour, Sarason, and others that the zona glomerulosa remains intact in the hypophysectomized animal, while the inner zones atrophy; in such an animal the sodium-potassium balance is maintained, indicating that the secretion of the glomerular zone is adequate for maintaining the electrolyte balance. Sarason and others have shown that in animals which have been given injections of desoxycorticosterone, which is a potent sodium-retaining agent, there is atrophy of, and depletion of, lipids in the glomerular zone. From these two lines of evidence one might suspect that the zona glomerulosa regulates the electrolyte metabolism.

The observations made in the animal experiments carried out in this study support this theory in general. When there is a great need for sodium-retaining hormone, because of low intake of sodium, the cholesterols of the zona glomerulosa

and outer zona fasciculata become depleted, since the excess hormone formation uses up the reserve cholesterols. This evidence indicates that the sodium-retaining hormone is produced in these zones.

The findings in the potassium-depleted animals are more difficult to explain if one follows the current concept that the concentration of the interstitial and plasma potassium is maintained through an antagonistic effect of the sodium concentration. Perhaps the glomerular zone secretes a potassium excretion factor. (Arch. Path., June '48 - J. Nichols)

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Study on the Mechanisms of Desoxycorticosterone Action: The role of sodium as an accessory factor in hypertension and nephrosclerosis has been emphasized during the past half century by an increasing accumulation of human and animal data. Inasmuch as sodium metabolism is regulated primarily by the adrenal corticosteroids, the possibility exists that the aggravation of the hypertensive states by salt results from their underlying etiologic basis in adrenal cortical dysfunction.

The hypertensive capacity of the adrenal corticosteroids is evident in the blood pressure elevations which attend adrenal cortical tumors. Its independence of sensitizing procedures as necessary adjuncts has been demonstrated and confirmed experimentally by investigations in which implantation of DCA (desoxycorticosterone acetate) pellets was followed by the development of hypertension in normal animals to which no supplementary sodium was administered.

These observations have prompted further study to determine first, if maximal increases in salt exchange could provoke hypertension in the absence of adrenocortical dysfunction and second, if the degree of hypertension induced by excessive salt-retaining hormone could be correlated with an increased level of salt intake.

It was found that increased sodium intake in rats up to two percent of body weight per day was accompanied by elevation of fluid exchange, increased heart and kidney weight, and reduction in growth rate, but did not provoke hypertension. The data indicate that increased velocity of fluid exchange represents a mechanism for augmenting the renal excretion of sodium, even under circumstances in which the increase in velocity entails further intake of a salt-containing solution.

The primary effect of DCA was to elevate the level of fluid exchange over control values by a ratio fixed by the dose of the drug and the amount of supplementary salt administration. Hypertension was a subsequent development. The

magnitude of DCA-induced hypertension did not correlate with the level of salt exchange, although it was augmented by salt administration, particularly at low DCA dosage levels. The effects of salt supplementation of DCA-implants on heart and kidney weight and on survival were disproportionate to the measured augmentation of blood pressure elevation. The resemblance between the action of salt in the DCA-induced hypertension of animals to that in essential hypertension lends additional support to the hypothesis that the mechanism of sustained pressure elevation in the human involves increased activity of the adrenal cortex. The favorable survival time of DCA-treated animals, once the period of most intense drug action had been passed, suggests the possibility of arresting human hypertensive disease either by removal of the adrenal cortex or by nullification of the activity of its salt-retaining steroids. (Am. J. Physiol., Sept. '48 - D. M. Green et al.)

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Blood Pressure and the Suprarenal Cortex: When it first became clear that the suprarenal had some part in the production of hypertension, the association seemed fairly straightforward. French workers, for instance, claimed that hypertension was accompanied by hypertrophy of the gland. This was not confirmed, and attention shifted to epinephrine itself. Later, the vital role of the cortex was revealed, and within ten years the research of American and Swiss workers culminated in the isolation and synthesis of a series of cortical hormones. Of these the most important was desoxycorticosterone with its specific action in raising the blood pressure. The intensive work on Addison's disease prompted by observation of the potent action of cortical extracts in this previously fatal condition, brought to light the prime importance of the sodium and potassium ions; and it was immediately asked whether the blood pressure changes in Addison's disease were due directly to lack of cortical hormones or to disturbance in the electrolyte pattern of the tissues. This question was almost immediately overshadowed by the experimental observations of Goldblatt and his associates on the effect of renal ischemia in producing hypertension.

Probably what is vaguely described as essential hypertension is a collection of conditions. Four factors clearly take leading parts - epinephrine, one or more of the hormones of the suprarenal cortex, the sodium and potassium ions, and renin - but how these factors combine in any one case is not understood. Perera and his colleagues have reported the development of hypertension in 8 out of 24 patients with Addison's disease under protracted treatment with desoxycorticosterone acetate. As an interesting corollary, Perera has recorded the case of a hypertensive patient who developed Addison's disease; with desoxycorticosterone therapy the hypertension continued, but when the condition was treated with salt alone the blood pressure fell to normal, even though with both treatments a normal serum-sodium was maintained. He has also shown: (1) that

while the subcutaneous administration of desoxycorticosterone acetate for a week to normotensive patients had no effect upon the blood pressure, its administration to hypertensive subjects for from 1 to 4 days raised the pressure; and (2) that this pressor action in hypertensive subjects was prevented by the rigid restriction of sodium-chloride intake, which also caused a slight decrease in resting blood pressure. The pressor action of desoxycorticosterone acetate in the hypertensive patients has been confirmed by Goldman and Schroeder, who gave this substance intravenously. They also found that in normotensive subjects it had no effect upon blood pressure. Selye noted in desoxycorticosterone-treated animals an increase in the serum sodium/chloride ratio; he later observed this increase in some hypertensive but never in normotensive persons. Arising from this, he recorded apparent benefit from the treatment in hypertension with ammonium chloride 6 Gm. daily, particularly in cases in which the serum sodium/chloride ratio was raised. Finally, it has been reported that in 4 out of 6 patients with hypertension a severely restricted salt intake causes a fall in blood pressure. (Lancet, 18 Dec. '48 - Annotation)

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Rubella - Experiments with Human Volunteers: During the last decade, rubella (German measles) has changed from a trivial infection of minor medical interest to an important public health problem. This is due entirely to the recognition in Australia of the fact that infection of a woman in the early months of pregnancy was liable to be followed, in a high percentage of cases, by serious damage to the infant, notably cataract and nerve deafness.

An epidemic at Flinders Naval Depot was brought to the attention of Prof. F. M. Burnet by Surgeon-Captain L. Lockwood, and a cooperative study of the virus was undertaken. From suitable patients blood and throat washings were obtained and stored in dry ice. Intensive efforts were made by Doctors Burnet and S. G. Anderson to cultivate the virus in chick embryos by various routes and at various ages. No lesions were observed, nor were positive complement fixation reactions obtained using material from these chick embryos as antigen and human convalescent serum. Negative complement fixation results were also obtained with concentrated throat washings as antigen.

This epidemic in naval ratings provided an almost unique opportunity to obtain a large supply of convalescent serum. From 2 to 5 weeks after their infection 55 volunteers each gave a pint of blood. A concentrated gamma globulin was produced, and the potency checked indirectly by showing that influenza virus antibodies had been concentrated to the calculated degree. This immune globulin has been used to prevent infection in women who have been exposed to rubella at a vulnerable stage of pregnancy. The serum was administered in 22 instances of proved or possible contact and in none of these cases was a rash subsequently observed. It was stressed that these findings could not be regarded

as wholly reliable; the serum was given at request whenever a reasonable likelihood of contact was reported, and the absence of a subsequent rash was mostly based only on the recipient's statement.

Experimental studies on the virus have been made, using volunteer human subjects, most of whom were University women students. Infection was induced by inhalation of atomized throat washings; later a more effective atomizer, using compressed air, was used. In the latter experiments, 9 infections were produced in 16 subjects, and since none of the other 7 who were in very close contact with the infected subjects developed rubella as secondary cases, it is felt that this dosage was fully effective with all susceptible individuals.

From 7 to 10 days after being inoculated the volunteers went into residence in Fairfield Hospital, Melbourne, where they were under daily observation for temperature and leucocyte count, as well as for lymph node enlargement and rash.

These experiments were under the control of Dr. Anderson, whose results may be summarized as follows:

1. Rubella can be readily transmitted to susceptible human subjects by inhalation of infective droplets.
2. The virus is present in high concentration in washings from the throat taken at the height of the rash.
3. Virus in throat washings (saline plus serum-broth) can be preserved in fully active state for at least 3 months at the temperature of solid CO_2.
4. The virus is unaffected by high concentrations of penicillin.
5. The incubation period to the appearance of the rash ranged from 13 to 20 days with a mean of 15.9 days.
6. The disease produced by inoculation was transmissible by ordinary contact to susceptible subjects.
7. None of the nine subjects giving a past history of rubella developed symptoms after inoculation, either as primary or secondary cases.
8. The existence of immunity as a result of past subclinical or unnoticed rubella can be deduced from the failure to infect a number of girls giving no history of past infection.

To a considerable extent these findings merely confirm what could be deduced from clinical and epidemiological observations, but they provide certain information that may be of great practical value. In the first place, virus can be obtained at will, stored indefinitely, and used to produce an infection when desired. Secondly, past clinical or subclinical infection provides at least a majority of individuals with an immunity, against what was probably a most abnormally heavy infecting dose, for at least five years. It should be possible, therefore, by inducing infection in a young woman, to guarantee the virtually complete elimination of the chance of infection during any subsequent pregnancy. (Excerpts from Annual Report, 1947-48, of the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, Prof. F. M. Burnet, Director. Request for this material was made to S. G. Anderson, now a Fellow in the Department of Preventive Medicine of the School of Medicine of Western Reserve University.)

TABLE I - INCIDENCE AND RATES PER 100,000 FOR ANEMIA, BY TYPE AND YEAR, 1942-1947

DIAGNOSIS	TOTAL		1942		1943		1944		1945		1946		1947	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Total	2,215	18.6	125	15.0	574	27.2	708	21.1	606	16.5	144	10.9	58	9.9
Anemia, sickle cell	63	0.5	2	0.2	10	0.5	24	0.7	20	0.5	6	0.4	1	0.2
Anemia, pernicious	113	1.0	5	0.6	27	1.3	35	1.0	31	0.8	11	0.8	4	0.7
Anemia, secondary	1,459	12.3	94	11.3	440	20.9	467	13.9	371	10.1	65	4.9	22	3.7
Anemia, splenic	42	0.4	7	0.8	12	0.6	13	0.4	9	0.2	1	0.1	-	0
Anemia, n. e. c.	375	3.2	11	1.3	47	2.2	115	3.4	130	3.5	46	3.5	26	4.4
Jaundice, hemolytic	163	1.4	6	0.7	38	1.8	54	1.6	45	1.2	15	1.1	5	0.8

Incidence of Anemia in the Navy and Marine Corps: The occurrence of cases of anemia in the Navy and Marine Corps is worthy of special study because of the manpower loss resulting from the high number of sick days per case and the high rates of invalidings from the Service.

During the 6 years 1942 through 1947, which includes the war years and the immediate post-war period, there were 2,215 cases of anemia reported among Navy and Marine Corps personnel. The incidence includes those cases admitted as A's (New Admissions), ACD's and AD's (Admitted Contributory Disability and Additional Diagnosis) and also those cases which had existed prior to the individual's entry into the Service (EPTE's). All of the data are based upon the Fa-Card (Individual Statistical Report of Patient). Of the various types of anemia included in the 6-year period, secondary anemia was the most important from the standpoint of numbers involved, 1,459 cases of this condition being reported, comprising more than 65 percent of all the cases of anemia.

It may be noted in Table I that the highest incidence rates for this group of diagnoses were reported in 1943, when the annual incidence rate for all of the conditions combined was 27.3 per 100,000 strength. Since 1943, there has been a decrease in the rate each year, that for 1947 being 9.9 per 100,000 strength. This decline in the overall incidence rate for the anemias in recent years is a reflection, principally, of the decrease in the rate for secondary anemia, which declined from a high in 1943 of 20.9 per 100,000 strength to 3.7 in 1947.

The distribution of the incidence of anemia by sex may be noted in Table II. Although the average incidence rate for all types of anemia for male personnel of the Navy and

Marine Corps for this six-year period is 16.8 per 100,000 strength, which is considered to be fairly low, the average incidence rate for female personnel is 101.8 per 100,000 strength. Secondary anemia is the condition mainly responsible for this variation in the rates for the two sexes. Other and unspecified types of anemia (listed in the table as anemia, not elsewhere classified), is also responsible for a part of the difference between male and female personnel in the total rate for the anemias.

TABLE II - INCIDENCE AND RATES OF ANEMIA, BY TYPE AND SEX, 1942-1947 COMBINED

DIAGNOSIS	TOTAL INCIDENCE		MALE PERSONNEL		FEMALE PERSONNEL	
	Number of cases	Average Annual Rate per 100,000	Number of cases	Average Annual Rate per 100,000	Number of cases	Average Annual Rate per 100,000
Total	2,215	18.6	1,947	16.8	268	101.8
Anemia, sickle cell	63	0.5	63	0.5	-	0
Anemia, pernicious	113	1.0	107	0.9	6	2.3
Anemia, secondary	1,459	12.3	1,249	10.8	210	79.7
Anemia, splenic	42	0.4	41	0.4	1	0.4
Anemia, n. e. c.	375	3.2	328	2.8	47	17.8
Jaundice, hemolytic	163	1.4	159	1.4	4	1.5

A distribution of the incidence of anemia by age group may be observed in Table III. More than 70 percent of all the cases of anemia were in individuals who were under the age of 30, almost 40 percent being in the age group from 20 to 24 years. However, when the incidence is correlated with the strength of the Navy and Marine Corps in each of the age groups, it is found that the rate is highest in the age group from 40 to 44 years. An average annual rate over the entire period of 37.5 per 100,000 strength was reported in this group as compared with an average annual rate of 19.2 in the age group from 20 to 24 years. There was a sharp drop in the incidence rates in the groups after age 44.

A length of service distribution indicates that almost 90 percent of all the individuals who had anemia during the war years and immediate post-war period had less than four years of service, more than 30 percent having less than one year of service. These data are presented in Table IV.

TABLE III - INCIDENCE OF ANEMIA, BY TYPE AND BY AGE GROUP, 1942-1947 COMBINED

DIAGNOSIS	AGE GROUP										
	Total all ages	Under 20	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60 and over
Total	2,215	318	880	378	218	208	93	64	33	19	4
Anemia, sickle cell	63	25	27	5	3	2	-	1	-	-	-
Anemia, pernicious	113	5	14	14	15	21	11	18	9	3	3
Anemia, secondary	1,459	181	609	273	136	129	63	36	19	12	1
Anemia, splenic	42	11	10	4	5	6	4	2	-	-	-
Anemia, n. e. c.	375	56	145	54	44	46	14	7	5	4	-
Jaundice, hemolytic	163	40	75	28	15	4	1	-	-	-	-

TABLE IV - INCIDENCE OF AMENIA, BY TYPE AND BY LENGTH OF SERVICE, 1942-1947

DIAGNOSIS	LENGTH OF SERVICE							
	Total	Under 3 mos.	3-5 mos.	6-11 mos.	1-3 yrs.	4-10 yrs.	11 yrs. and over	Unspecified
Total	2,215	147	155	374	1,262	139	132	6
Anemia, sickle cell	63	12	16	9	22	2	1	1
Anemia, pernicious	113	6	10	18	48	11	19	1
Anemia, secondary	1,459	85	92	243	873	84	80	2
Anemia, splenic	42	6	6	4	18	4	4	-
Anemia, n. e. c.	375	14	21	71	213	27	27	2
Jaundice, hemolytic	163	24	10	29	88	11	1	-

The incidence of anemia distributed by race is shown in Table V. It may be noted that the over-all incidence rate during the six years 1942 through 1947 was higher for nonwhite personnel. This higher rate was due to the comparatively large number of cases of sickle cell anemia among nonwhite personnel.

TABLE V - INCIDENCE & RATES OF ANEMIA, BY TYPE AND BY RACE, 1942-1947 COMBINED

DIAGNOSIS	WHITE PERSONNEL		OTHER PERSONNEL	
	Number of cases	Average annual rate per 100,000	Number of cases	Average annual rate per 100,000
Total	2,070	18.3	145	24.5
Anemia, sickle cell	11	0.1	52	8.8
Anemia, pernicious	111	1.0	2	0.3
Anemia, secondary	1,397	12.4	62	10.5
Anemia, splenic	41	0.4	1	0.2
Anemia, n. e. c.	352	3.1	23	3.9
Jaundice, hemolytic	158	1.4	5	0.8

(Statistics of Navy Medicine, Feb. '49)

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Relationship of Diarrheal Disease to Faulty Eductor System of Scullery Equipment: Two epidemiological reports received from a Light Cruiser, operating in the Mediterranean in November 1948, contained descriptions of an outbreak of diarrheal disease, associated with the ports of Marseille, France, and Leghorn, Italy. Initial evidence indicated the possibility and subsequent evidence tends to confirm that faulty operation of the eductor system of the scullery equipment resulted in the contamination of the sinks and dishwashers with polluted harbor water, and that this may have been responsible for the outbreak because organisms cultured from the stools of several ill patients and from the residual water of the dishwashing machine were identified as Shigella dysenteriae.

The eductor system is based upon the principle that a mass of water in a pressure main passing a nozzle-like constriction in the main creates a suction about the nozzle. The suction acting upon fluid contained in another lower pressure line, leading to the nozzle, causes a flow from the lower pressure line into the pressure main. This device is used to move waste water from a lower level to an above-the-water-line discharge point.

The following factors influence the efficiency of the eductor system:

1. Corrosion of the eductor nozzle.
2. Diminished pressure in the main.
3. Clogging of the eductor system with food scraps.
4. Improper handling of regulating valves, e.g., opening of the eductor line prior to the development of pressure in the main.

Failure of the eductor, due to one or several reasons, results in the back-flow of water from the main into the system which it is designed to drain. In the case of scullery equipment, contamination with sea water results. This may not have serious consequences at sea, but in ports, harbor water is often little better than raw sewage.

The contamination of scullery and commissary equipment by polluted harbor water as a result of faulty operation or defective eductor systems creates one more means for the spread of gastro-enteric disease.

Attention should be directed toward eliminating this eductor system hazard in addition to the other possible and probable sources of gastro-enteric disease. (Preventive Medicine Div., BuMed)

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Black Widow Spider Bites - Effect of Calcium Gluconate in Six Cases: The syndrome following the bite of a black-widow spider, arachnidism, is a definite clinical entity in the field of general medicine. The belief that the bite of this spider, Latrodectus mactans, present in all but seven states of the U. S., is poisonous for man has been recognized for centuries. Before Bogen's review of the literature in 1926, there was much skepticism attached to the fact that such a small creature could, by its bite, produce terrifying generalized symptoms in man. He reported 380 cases with 17 deaths, in eighteen states.

D'Amour et al. reported that the black widow spider is greatly increasing in numbers in the vicinity of human habitations - not only in outdoor privies, but also in beds, garages, automobiles, tents, and even high in office buildings.

Knowledge of the clinical entity is important since many spider victims are subjected to needless operations because the symptoms often simulate acute surgical conditions of the abdomen. An appalling record of human suffering has been checked back to L. mactans and its prototypes.

The cases of arachnidism reported represent but a small fraction of the actual number that have occurred. Curtailment of the arachnid menace in an indigenous area can only be accomplished by unified efforts of human beings and parasitic enemy insects of the black widow spider.

Evidence for the incidence of arachnidism rests largely on the statements of patients who have been bitten and whose description of the spider fits the characteristics of L. mactans. In numerous cases, the spiders have been caught and identified with certainty.

L. mactans has been found in dark corners and in clothes closets. They are cannibalistic, feeding on each other whenever the opportunity presents itself. The nickname "black widow" given to the female of the species arises from its habit of capturing and feeding on the much smaller male after he has served the ends of species preservation. The globose abdomen of the female stands out like a highly polished black pearl. It is attached by a slender pedicle to the smaller cephalothorax. The body averages 1.27 cm. in length. The abdomen is about 0.9 cm. in length. Slender pointed legs when expanded have a span of from 3.8 to 5.1 cm. Legs and body are a glossy black and are covered by short black hairs. On the ventral surface of the abdomen there is a rich red marking resembling an hourglass. Dorsal to the spinnerets in the midline of the convex surface of the abdomen is an additional red marking. The full-grown female, particularly when distended with eggs, appears, from experiments with animals, to be the most poisonous. It is, however, a timid creature, and when disturbed, makes every effort to escape; this explains the relatively few bites in spite of the prevalence of this arachnid. When cornered or compressed, as between skin and clothing, the spider bites in self-defense. The male is ignored as an etiologic factor of any importance because of its size, timidity, and scarcity.

The potent nature of the venom is readily appreciated through observing a victim about an hour after a bite. The victim writhes in agony, terror-stricken, and expressing fears of death. Thesing states that the venom of the female of this species is fifteen times as potent as that of a rattlesnake. The venom has been stated to be a toxalbumin with its most damaging activity on nerve endings. It is a thick, translucent, oily, lemon-yellow fluid, which is acid in reaction, and from which a hemolysin and arachnolysin have been isolated.

Blair, in 1933, allowed a black widow spider to bite him in an experimental study and recorded careful clinical observations dividing the clinical picture into three stages: the stage of lymphatic absorption of the injected venom, characterized chiefly by pains in the bitten area and absence of systemic effects; the stage of vascular dissemination, characterized, clinically, by the explosive onset of widespread agonizing muscular pains and a condition of profound shock depending on the quantity of the venom or its toxic products; and the stage of elimination of the venom or its toxic products, characterized clinically by hypertension, diaphoresis, gradually diminishing muscular pain, and evidence of renal damage - this stage is suggestive of an acute toxic nephritis.

The syndrome, as presented by 6 patients bitten by the black widow spider observed in a seven-day period in an overseas tropical area, usually followed

a similar pattern: transient excruciating local pain at the site of the spider bite, rapid local edema, and redness of the skin at the site - in 2 cases the site could not be identified; in from 10 to 15 minutes a "burning sensation" that spread centrifugally from the site of the bite and soon involved the whole body, passing off in about from 20 to 30 minutes; a sudden abdominal pain, often cramp-like as in an acute surgical condition of the abdomen; cramp-like pains in the legs, arms, and back; a general feeling of "utter weakness"; restlessness and extreme fear reaction, often hysteric; headache, nausea, and vomiting; and burning of the soles of the feet (in bites of unknown types this symptom may be pathognomonic).

A board-like abdomen, nontender to palpation, was present in each of these 6 cases; there was hypersensitivity of the skin; the calf muscles were tender to palpation; 2 patients were in profound shock with blood pressure unobtainable (the other 4 patients had normal or slightly elevated blood pressures); motion of extremities was limited by muscle spasm, and flexion was a prominent feature; the temperature was normal or only slightly elevated; the pulse was slow, being 80 or under in all cases; examination of the blood showed a moderate leukocytosis; and the 2 patients presenting a picture of profound shock showed albuminuria.

One patient described his episode as follows: "I was putting on my shirt this morning when I felt as if someone had stuck a needle in my shoulder. When I tore off my shirt a black spider with a red-orange spot on its belly fell out. The place stung for about 10 minutes, and then a burning sensation spread all over my arm and soon over my whole body. I began to get stomach cramps and my legs ached. Soon I felt weak and dizzy and wanted to sleep but headache and a feeling of terrible nausea came over me."

The patients in this series were immediately given 10 c.c. of 10 percent calcium gluconate intravenously. Subsequently, they were given a saline infusion containing 10 c.c. of 10 percent calcium gluconate. An ice bag was applied to the affected area. Relief was obtained in a short time in all cases and was followed by profound sleep. The patients were out of bed the next day and back to duty on the fourth day. Even the 2 patients in profound shock responded. No morphine was used, and antivenin was not available.

Blair believes that the condition of shock, characteristic of the second stage, suggests the presence of a histamine-like substance in the spider venom. The clinical picture of the development of an acute toxic nephritis has caused much speculation. Other observers considered the syndrome to be like hypertension in the adult and eclampsia in the child (children often have convulsions in arachnidism). Albuminuria was present in four of the 29 cases reported by Walsh and Morgan and in 2 of this series. These findings may be similar to the "allergic nephritis" seen after bee stings.

Intravenous magnesium sulfate, until symptoms of spider poisoning have disappeared, has long been recommended and seemed rational in cases in which hypertension was a prominent factor. Frawley and Ginsburg had good results with magnesium sulfate in 11 cases, with freedom from symptoms in twenty-four hours. Hypertonic glucose has been used with varying results. Morphine sulfate in heavy dosages has frequently been relied upon for relief by some physicians. The results of Gray's observations with convalescent serum seem to bear out the suggestion that antivenin is developed by the patient recovering from the bite of the black widow spider. It is reasonable to suppose that it would be effective in spider-bite poisoning. Antivenin (L. mactans) is listed in New and Non-Official Remedies. It is standardized on the basis of its ability to neutralize the venom of the black widow spider when the two are injected simultaneously in mice. Gilbert and Stewart reviewed previous therapeutic measures in the treatment of arachnidism and presented 5 cases in which intravenous solution of 10 percent calcium gluconate gave instant and prolonged relief of pain and also produced relaxation of muscular spasm. The intramuscular route was recommended and used in children, with almost immediate relief. Calcium lactate was ineffective orally, probably because of its incomplete and slow absorption. In the series reported in this article intravenous calcium gluconate was found to give immediate and prolonged relief of muscle spasm and pain in all cases, and it is believed that this is the best available therapy in conjunction with other supportive measures. Some workers have remarked on the relief given by frequent hot baths. (New England J. Med., 6 Jan. '49 - W. E. R. Greer)

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Oral Color Photography as a Means of Personnel Identification and Registration of Oral Lesions and Deformities: In dentistry, there is a need for some method of recording accurately the appearance and physical condition of the oral tissues. The method most commonly used by the military services, dental colleges, and private practitioners is that of recording various fillings, missing teeth, prosthetic replacements and other dental conditions on a printed chart. Although affording much valuable data, charting methods are subject to error and are limited in their true depiction of the dental arches and their surrounding structures.

An apparatus for taking intraoral 35 mm. color photographs of anterior teeth and full upper and lower dental arches is described and illustrated. This apparatus, constructed to meet the requirements of mass intraoral photography, is easily operated by inexperienced personnel and can be used to photograph approximately 150 subjects daily. It utilizes metal mouth mirrors that can be removed readily for sterilization in steam or boiling water. Adjustable identification numbers are recorded on each side of all photographs to identify the subject positively. Lights, viewing mirror, and exposure mechanism are operated automatically by a single lever. Exposure time and focusing of the camera are predetermined and remain constant for all photographs. (NM 012 004 (X-767), Rep. No. 2, 28 Oct. '48, Nav. Med. Res. Inst., NNMC, Bethesda, Md. - B. L. Taylor and C. A. Schlack)

Need for Reserve Medical Officers as Stationkeepers in the Naval Air Reserve Training Program: Reserve medical officers are needed for full-time active duty as "Stationkeepers" at the following Naval Air Reserve Training Stations and Naval Air Reserve Training Units:

Naval Air Station .....Birmingham, Alabama
" " " .....Columbus, Ohio
" " " .....Denver, Colorado
" " " .....Grosse Ille, Michigan
" " " .....Minneapolis, Minnesota
" " " .....Magna Falls, New York
" " " .....St. Louis, Missouri
" " " .....Spokane, Washington
Naval Air Reserve Training Unit....Seattle, Washington
" " " " " ....Jacksonville, Florida

Applications are desired from both Reserve flight surgeons and general medical officers. Those who qualify will receive the full pay and allowances of their rank while serving on active duty. In addition, those who volunteer to remain on active duty one year or longer will receive the additional compensation of $100 per month provided by Public Law 365 of the Eightieth Congress.

Application should be made to the Chief of Naval Personnel, Navy Department, Washington, D. C., via (1) The Chief of Naval Air Reserve Training, Naval Air Station, Glenview, Illinois, and (2) The Chief of the Bureau of Medicine and Surgery. (Personnel Div., BuMed)

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BUMED CIRCULAR LETTER 49-6 1 February 1949

To: All Holders of the Manual of the Medical Department

Subj: Advance Change 3-8, MMD

Encl: 1. (HW) Subject Change

1. The enclosed Advance Change 3-8 is effective immediately. It shall be recorded on the "Record of Changes" page in the Manual. The individual paragraph changes are to be inserted in their proper places in the Manual text. At a later date, these changes will be incorporated in printed page change 3.

--BuMed. H. L. Pugh

Note: Enclosure consists of 30 pages.

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BUMED CIRCULAR LETTER 49-7 2 February 1949

To: Medical Officer in Command, All Naval Hospitals

Subj: Hospitalization of Veterans Administration Patients with Service-Connected Disabilities in Naval Hospitals; Report of

Ref: (a) Veterans Administration Manual, M10-3, Change 8, Paragraph 85.1.

Encls: 1. (HW) Copy of Veterans Administration Form Letter, FL 10-59.
2. (HW) Copy of Veterans Administration Form Letter, FL 10-60.

1. Subparagraph (a) of reference (a) is quoted in part as follows for information:

"A total disability rating will be assigned without regard to the provisions of the Rating Schedule when it is established that a service-connected organic disease or injury by reason of an exacerbation has developed actual total incapacity which has required hospital treatment for a period in excess of 21 days. Similarly, a total rating will be assigned, without regard to the provisions of the Schedule, when a service-connected organic disease or injury has developed pathological manifestations of such character as to require surgical intervention, which, with symptomatology referable to the service-connected condition, has resulted in total occupational incapacity and hospitalization for a period in excess of 21 days. Accordingly, in any case where a service-connected organic disease or injury meets the above requirements, the rating will be increased to 100 percent effective during a period of hospital treatment immediately following a period of continuous hospital treatment of 21 days. This increase is to be based upon the report of hospital treatment and examinations to be furnished as of the 21st day of continuous hospitalization for treatment, in the form of an interim summary, prepared in the same outline as the Final Summary (VA Form 10-2614) as set forth in VA Technical Bulletin TB 10A-99. No pass or authorized leave of less than 30 days will be considered as interrupting the continuity of hospitalization during the first 21 days or thereafter."

2. In the administration of the above regulation by the regional offices of the Veterans Administration, enclosure 1 will be forwarded to a naval hospital by the regional office whenever patients coming within the provisions of reference (a) are admitted to naval hospitals. On the 18th day of hospitalization of such patients in naval hospitals, the regional office will send the medical officer in command a copy of enclosure 2. On the 21st day of hospitalization of such patients in naval hospitals, the medical officer in command will furnish the regional office of the Veterans Administration the information requested in enclosure 2.

3. Attention is invited to the fact that the responsibility for determining the eligibility of increased Veterans Administration benefits under the provisions of reference (a) rests with the regional office of the Veterans Administration and that the duty of the medical officer in command in respect to this determination is limited to submission of the required information on the 21st day of hospitalization.

--BuMed. C. A. Swanson

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